

Peritoneal dialysis-associated peritonitis

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Abstract

Peritoneal dialysis is used worldwide as a treatment for end-stage kidney failure. Globally, it accounts for about 11 % of all therapeutic dialysis interventions, with over 200.000 patients currently undergoing the procedure in more than 130 countries. In Slovenia, however, the percentage of patients treated by peritoneal dialysis has fallen due to the rise in renal transplantation services and the number of transplanted patients with functioning kidney graft. In 2013, patients receiving peritoneal dialysis in Slovenia accounted for only 2.5 % (52 patients) of the total number treated by renal replacement therapy (2077 patients).

A potential complication of peritoneal dialysis is peritonitis. Although in general, peritonitis-related mortality has declined significantly in the last decade (with less than 5 % of peritonitis episodes resulting in death) possibly due to improved preventive measures, peritonitis still remains a direct or major contributing cause of mortality in approximately 16 % of peritoneal dialysis patients.

In these patients, the time frame between the onset of peritonitis and the commencement of treatment critically determines the course and outcome of the disease. Peritonitis patients require urgent care, and therapeutic interventions may include conservative and/or surgical treatment protocols.

Meanwhile, it is important to emphasize that prevention of peritoneal dialysis-associated peritonitis is as important as early diagnosis and timely treatment.

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1 Introduction

Peritonitis is acute inflammation of visceral and parietal layers of peritoneum, which can severely affect the patient and be even life-threatening. Due to the high concentration of bacteria in the gastrointestinal tract, and large peritoneum surface, it often leads to sepsis (1,2). Ever since peritoneal dialysis (PD) was introduced after 1960, peritonitis has been a serious complication that damages the

peritoneal membrane and causes structural and functional changes. It is the most common cause of hospital admission and the removal of peritoneal dialysis catheter, and the reason for discontinuing peritoneal dialysis in 30–80% of cases. In Slovenia, peritonitis incidence is estimated to stand at about 0.33 episode per patient-year of treatment (one

episode every 36 months of the patient's treatment) (3-6).

2 Peritonitis

Peritonitis is the inflammation of visceral and parietal layers of peritoneum due to various reasons. Based on the cause and mechanism of formation, peritonitis can be classified as primary, secondary or tertiary (1,2). Primary peritonitis, which represents about 10% of all peritonitis cases, is rare inflammation of peritoneum with no pathological changes proven in the abdomen. It most frequently affects children, patients with cirrhosis and ascites, people with nephrotic syndrome and patients with congestive heart failure (2,7). Secondary peritonitis, which is more common (about 80% of the cases), is infection caused by an injury or inflammation in the abdominal cavity. Secondary peritonitis most frequently occurs in patients with peptic ulcer disease, acute appendicitis, acute cholecystitis, and diverticulosis (2,8), and also occurs as a complication in PD patients. The etiopathogenesis of peritonitis caused by PD is described below. Tertiary peritonitis (approximately 10% of the cases) is the infection of peritoneum with low virulent bacteria or fungi, which persists even though the abdominal origin of sepsis has been cured. It is most frequent in immunocompromised patients (1,8,9).

Patients with peritonitis require conservative and/or surgical treatment. Peritonitis is treated by eliminating the origin of infection, rinsing the abdominal cavity with a 0.9% NaCl solution, and introducing first empiric and then targeted antibiotic therapy. Post-operative intensive care with fluid infusions, electrolyte replacement, correction of metabolic disorders and vital organs support can contribute critically to the successful

outcome of the treatment. It is vital to suspect peritonitis as soon as possible, confirm the diagnosis and immediately start the treatment. The time between the onset of peritonitis and the commencement of treatment critically determines the course and outcome of the disease (1,2,10-13).

3 Epidemiology

Peritoneal dialysis is used worldwide as a treatment for end-stage kidney failure. Globally, it accounts for about 11% of all therapeutic dialysis interventions, with over 200,000 patients currently undergoing the procedure in more than 130 countries (14). In USA, their number stands at around 26,000 (15). The prevalence and share of patients treated with PD in Slovenia have decreased over the past decade, dropping considerably under the global average of 11% (16). In 2013, only 52 patients (2.5%) of the total 2077 patients treated by renal replacement therapy were receiving PD in Slovenia. The percentage of patients treated by PD has fallen primarily due to the increasing share of patients with a functioning kidney graft (32.5% of all patients) (17).

The incidence of peritonitis in the first years after introducing PD was very high, it however dropped significantly after several preventive measures were introduced. In the USA, the incidence of peritonitis in PD patients in the 1980–1990 period was 1.1–1.3 episode per patient-year of treatment, while recent studies have reported the incidence of 0.4 episode per patient-year of treatment (4).

Although the incidence of peritonitis has been decreasing in the past years, the data differ greatly between countries, as well centres within a country, with the reported incidence ranging from 0.06 to

1.66 episode per patient-year. The main reasons for such variation in incidence most probably lie in individual centre's failure to comply with recommendations for preventing peritonitis, differences in patient population, and inconsistently collected data. The International Society for Peritoneal Dialysis (ISPD) believes that the incidence of peritonitis should not exceed 0.5 episode per patient-year of treatment in any of the centres. In Slovenia, peritonitis incidence is estimated to stand at about 0.33 episode per patient-year of treatment (one episode every 36 months of the patient's treatment) (2-4,6,14,15,18).

To guarantee the quality of collected data, which can then be compared between institutions to assess the centres' quality of work, ISPD issued the following recommendations for recording peritonitis incidence in PD. Every centre performing PD should record annual incidence of peritonitis. It also recommends recording whether peritonitis occurred already in the hospital soon after placing the peritoneal dialysis catheter, or only after patients started home PD. When designing local recommendations for empiric antimicrobial therapy, data on the infecting organisms and their antimicrobial susceptibilities are essential. It is also recommended to record the number of patients who did not experience a peritonitis episode in the past year, and the number of deaths associated with peritonitis (deaths during hospitalization for a peritonitis episode or within 4 weeks of a peritonitis episode) (4).

4 Etiopathogenesis

There are several possible infection pathways:

- intraluminal – the infection occurs through the peritoneal dialysis catheter

following a contamination during bag exchange, or due to bacteria in the dialysis solution;

- periluminal – the infection occurs alongside the catheter though the abdominal wall;
- transmural – the infection occurs due to the translocation of enteric bacteria;
- ascending – the infection occurs, if the vagina and the peritoneal cavity are linked through fallopian tubes or fistulas;
- hematogenous.

Most infections occur through the intraluminal route. The periluminal pathway is a less common cause of infection due to the advancements and improvements in inserting dialysis catheters, as well as the use of double-cuff catheters that prevent the bacterial invasion to the peritoneal cavity. Other infection pathways are even less common (3,19,20).

Globally, some 75% of cases are caused by gram-positive bacteria, with the most common causes being *S. epidermidis* (30–50% of all infections) and *S. aureus*, which are normally present on skin and can enter the abdominal cavity through the intraluminal pathway due to unsterile manipulation of catheter junctions. Other common causes are coagulase-negative staphylococci, *E. coli*, *P. aeruginosa* and fungi (especially *Candida spp.*) (2,3,19). Etiological data vary somewhat depending on the geographic location, e.g., in India peritonitis is more frequently caused by infection with gram-negative bacteria than with gram-positive bacteria, which negatively impacts treatment outcomes. There are no significant differences in the causes of peritonitis occurring in hospitals or at home (19,21).

5 Clinical picture

Peritonitis is a common complication in PD. The most significant symptom of peritonitis is diffuse abdominal pain, and its most significant sign is cloudy dialysate (12,18). Cloudy dialysate is almost always a sign of infectious peritonitis, as other causes are extremely rare (e.g. chemical peritonitis, calcium channel antagonists, malignant disease, hemoperitoneum, etc.) (4). Severe peritonitis can also be accompanied by other symptoms and signs, such as elevated body temperature, nausea, vomiting, diarrhea, and poor dialysate outflow (3).

6 Diagnosis

To confirm a peritonitis diagnosis, two of the following three criteria must be met:

1. presence of clinical signs (e.g. abdominal tenderness or pain);
2. cloudy peritoneal effluent with leukocyte count over $0.1 \times 10^9/L$, more than 50% of which are neutrophils;
3. microbes proved in the peritoneal effluent (3,4).

To quickly determine whether peritonitis is caused by gram-positive or -negative bacteria, we may carry out gram staining of the effluent; however, the method has very low sensitivity, and only detects 10–40% of infected samples (2). Peritonitis should also be included in the differential diagnosis of a PD patient presenting with abdominal pain, even if the effluent is clear (4).

Imaging tests are not really relevant in determining the diagnosis, they are however very helpful in eliminating other potential causes of peritonitis that are possible based on the patient's clinical picture (11,12). If imaging tests show free air in PD patient's abdomen, this is an

independent risk factor for peritonitis, so the above listed tests must be carried out if the effluent is clear or cloudy to confirm or exclude peritonitis (22). The peritoneal membrane thickness, which affects the effectiveness of PD, can be evaluated using an ultrasound scan instead of invasive methods (23).

7 Treatment

When the probability of peritonitis in PD patients is very high or confirmed, we must examine the catheter exit site and determine whether there are any signs of inflammation. We then take an effluent sample and send it to testing. We should not delay, but immediately start empiric antibiotic therapy, since the postponement of treatment may critically affect the course and outcome of the peritonitis episode. ISPD recommends discontinuing PD for at least 6–48 hours after administering the first dose of the antimicrobial medicine. The opinions on this are split, since discontinuing PD means that the patient will require hemodialysis, which comes with its own set of risks and complications. Some authors thus recommend not to discontinue PD, unless the peritoneal catheter must be removed. For every patient we must assess whether they require additional treatment with analgesics, intraperitoneal heparin or antifungal prophylaxis. Before the discharge, the patient must be taught how to administer intraperitoneal medicine, and given regular follow-up appointments. It is reasonable to check whether PD is performed correctly, and to point out any potential mistakes to the patient. Initial management of peritonitis is presented in Figure 1 (4).

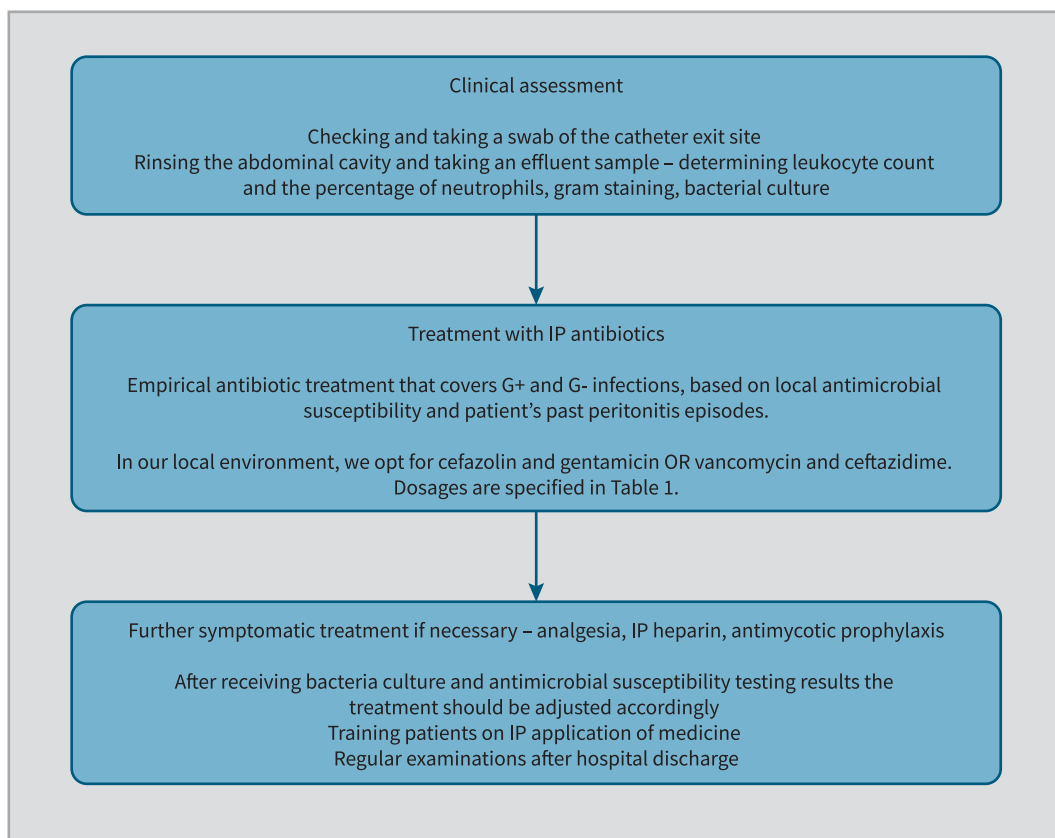


Figure 1: Initial treatment of peritonitis; IP – intraperitoneal; modified from ISPD guidelines (4).

7.1 Antibiotic selection and dosage

The initial empiric therapy should cover both gram-positive and gram-negative organisms. ISPD recommends covering gram-positive organisms by vancomycin or a first generation cephalosporin (e.g. cefazolin), and gram-negative organisms by a third-generation cephalosporin (e.g. cefepime, ceftazidime) or an aminoglycoside (e.g. gentamicin). The local spectrum of antibiotic resistance and the experience of the dialysis centre prevail over ISPD recommendations. In Slovenia, best outcomes have been recorded for intraperitoneal therapy with cefazolin and gentamicin (see Algorithm 1). After receiving the bacteria culture and antimicrobial sus-

ceptibility testing results, we adjust the treatment if necessary. We successfully cure around 75% peritonitis cases with only antimicrobial therapy and without any other measures. The success of antimicrobial therapy without catheter removal largely depends on the organism causing the infection, and is as follows: coagulase-negative staphylococci – 90%, *S. aureus* – 66%, gram-negative bacteria – 56% and fungi – 0%. If the patient's clinical status does not improve, and the effluent does not clear up in five days, the peritoneal catheter should be removed. In some cases we should not wait five days before removing the catheter; indications for removing the peritoneal catheter are described below. If the patient is at risk, is showing signs of sepsis and/or signs of infection of the catheter

exit site, a systemic antibiotic should be administered intravenously, empirically selecting vancomycin and ceftazidime, or an antibiotic based on the causes and antimicrobial susceptibilities. Recommended doses for intraperitoneal delivery of commonly used antibiotics are presented in Table 1 (2-4,19,24).

7.2 Treatment duration

The duration of treatment depends on the organism causing the infection. For recommended duration of treatment for individual organisms see Table 2 (3,4).

7.3 Evaluating treatment outcomes

After commencing the treatment, we regularly monitor patients and assess whether their clinical status is improving. We should expect an improvement of clinical status and partial clarification of the cloudy effluent within 48 hours of starting the treatment, at which point we determine the leukocyte count and the

percentage of neutrophils in the effluent. If their number does not drop after three days of treatment, the possibility that the treatment will be effective falls below 64% (11,25). In these cases, it is sensible to switch from intermittent to continuous antibiotic administration. If that is not possible, we should increase the dose and frequency of antibiotic delivery (11).

7.4 Indications for catheter removal and replacement

Sometimes antimicrobial therapy is ineffective in treating peritonitis, so we should consider removing the peritoneal catheter. Early removal after ineffective antimicrobial therapy decreases the mortality and the duration of peritonitis episodes. Indications for removing the peritoneal catheter are:

- refractory peritonitis (the patient does not respond to the antibiotic therapy as expected within 5 days);
- recurrent peritonitis (peritonitis recurring within four weeks);
- fungal or mycobacterial peritonitis;
- peritonitis accompanying other pathological conditions in the abdomen (e.g. abscess, perforation, etc.);
- culture-negative peritonitis with persistently elevated dialysis effluent leukocyte counts.

A new catheter may be inserted with recurrent peritonitis, if PD effluent becomes clear with initial therapy. In other cases, the catheter should be removed and a new one should not be inserted immediately, but only after a minimum of 2 weeks of therapy with an antimicrobial pharmaceutical. A new catheter should only be inserted 2–4 weeks after the removal, after complete resolution of peritonitis symptom (4,11,12).

Table 1: Dosing of antibiotics commonly used for the treatment of peritonitis in PD patients, modified from ISPD guidelines (4). LD – loading dose, MD – maintenance dose

Antibiotic	Intermittent (1 exchange)	Continuous (all exchanges)
Gentamicin	0.6 mg/kg daily	LD 25 mg/L, MD 12 mg/L
Amikacin	2 mg/kg daily	LD 8 mg/L, MD 4 mg/L
Cefazolin	15–20 mg/kg daily	LD 500 mg/L, MD 125 mg/L
Ceftriaxone	1,000 mg daily	no data
Cefotaxime	500–1,000 mg daily	no data
Ceftazidime	1,000–1,500 mg daily	LD 500 mg/L, MD 125 mg/L
Vancomycin	15–30 mg/kg every 5–7 days	LD 30 mg/kg, MD 1.5 mg/kg/bag

7.5 Adjunctive treatments and specifics

Some patients with PD-related peritonitis could be managed on an outpatient basis. The decision to hospitalize a patient depends on their hemodynamic

stability, and the severity of signs and symptoms. If the patient is affected by severe pain, they should be provided with a sufficient amount of analgesics. ISPD recommends systemic antifungal prophylaxis, since fungal infections are hard to treat, and virtually always re-

Table 2: The duration and specifics of treatment based on the organism causing peritonitis, modified from ISPD guidelines (4).

Organism	Recommendations
Coagulase-negative staphylococci	Treatment with IP cephalosporins or vancomycin, according to local antimicrobial susceptibility. Duration of treatment: 2 weeks.
Enterococcus spp.	Treatment with IP vancomycin. IP aminoglycosides for severe peritonitis. Duration of treatment: 3 weeks. *Exception: vancomycin-resistant Enterococcus (VRE) – treatment with IP ampicillin. If the organism is ampicillin-resistant, therapy based on antimicrobial susceptibilities (e.g. linezolid, teicoplanin, etc.).
Streptococcus spp.	Treatment with IP ampicillin. Duration of treatment: 2 weeks.
S. aureus	Treatment with locally effective antibiotics. Duration of treatment: 3 weeks.
Corynebacterium spp.	Treatment with locally effective antibiotics. Duration of treatment: 3 weeks.
Pseudomonas spp.	Treatment with 2 antibiotics with different mechanisms of action (e.g. IP gentamicin or oral ciprofloxacin with IP ceftazidime or ceftipime). Duration of treatment: 3 weeks. In the event of an exit-site infection, the catheter should be removed.
Other gram-negative bacteria	Treatment with locally effective antibiotics. Duration of treatment: 3 weeks.
Polymicrobial peritonitis	Enteric organisms If there is no response to the initial empiric therapy, we conduct diagnostic imaging (abdominal ultrasound, CT scans) and consult with a surgeon. Treatment with metronidazole, IP vancomycin and either IP aminoglycoside or IP ceftazidime. Duration of treatment: at least 3 weeks. Multiple gram-positive organisms Treatment with locally effective antibiotics. Duration of treatment: 3 weeks.
Culture-negative peritonitis	A repeat dialysis effluent analysis after three days of therapy. If effluent analysis results show improvement, we should narrow down the antibiotic therapy spectrum (e.g., replace aminoglycosides with a first-generation cephalosporin or vancomycin). Duration of treatment: 2 weeks.
Fungal peritonitis	Immediate catheter removal. Treatment with a locally effective antimycotic medication. Duration of treatment: at least 2 weeks.

quire catheter removal, and they most frequently occur during antibiotic therapy. For patients with cloudy effluent, the guidelines recommend heparin 500 units/L IP to prevent occlusion of the catheter by fibrin (4).

8 Prevention

Prevention of peritonitis remains a challenge, and is as important as early diagnosis and timely treatment. Every centre providing PD must regularly monitor and analyse peritonitis rate in patients, and provide adequate prevention measures (3,5,26).

ISPD's updated guidelines from 2016 give the following recommendations for preventing peritonitis in PD.

Dialysis catheter placement. Administering a parenteral prophylactic antibiotics dose prior to peritoneal catheter insertion has been proven to reduce early peritonitis incidence. Based on the conducted studies, the use of cephalosporins, gentamicin and vancomycin is recommended, and local susceptibility of bacteria must be considered when deciding on the antibiotic. At the University Medical Centre Ljubljana (UKC LJ), one 2 g dose of cefazolin 30–60 minutes before the surgical incision is used for antibiotic prophylaxis. Sometimes we prescribe a higher dose (3 g) to overweight patients (27,28). The catheter insertion technique does not affect peritonitis incidence (4,5,18,19,26,29). In the recent years, UKC LJ has only been using laparoscopy for inserting peritoneal dialysis catheters. We placed 22 catheters in 2016, without recording any major early complications (27).

Catheter design. There are several types and shapes of catheters – straight, curved and swan-neck. They are usually made from silicone, and sometimes from polyurethane. Most commonly

used catheters have two Dacron cuffs, which are anchored in the abdominal wall during the insertion to properly fixate the catheter (27). Several studies have compared peritonitis rate for straight and curved catheters, and found no significant difference (4).

Dialysis method. We use exclusively the double bag system, for which peritonitis rates are about 30% lower compared to other methods (3,4,6,18).

Training of patients and their family. Experienced dialysis staff must teach the patient and their family how to properly perform the peritoneal dialysis, since the quality of training greatly affects the rate of peritonitis. Unfortunately, there are no evidence-based recommendations clearly specifying when, where and how frequently such training should be provided. It is important that when the patient starts PD, nursing staff with experience in peritoneal dialysis visits them to check for potential mistakes and correct the patient (3-5,26).

Dialysis Solution. Several studies have examined the effect of different dialysis solutions in use. It is suggested that neutral-pH, low-glucose-degradation-product PD solutions are more biocompatible and lower the occurrence of peritonitis compared to other dialysis solutions. However, confirming these assumptions would require more research, and the currently held opinion is that the type of solution does not affect the peritonitis incidence (4,18,30).

Catheter exit site care. Daily topical application of antibiotic ointment to the catheter exit site is recommended. Proper hand hygiene is essential when performing the dialysis. Wearing a face mask is not obligatory, it is however recommended and advised (3-5).

Antibiotic prophylaxis before procedures. Due to the increased peritonitis risk in PD patients after procedures,

antibiotic prophylaxis is recommended prior to colonoscopy and invasive gynecologic procedures (4).

9 Prognosis

Although mortality rate in PD patients has decreased in the past years, the long-term survival is relatively low (11,15). While the one-year survival rate stands at 86%, the 10-year survival rate is only about 11% (15). There are several contributing factors to the low 10-year survival rate, which depends on the patient characteristics and factors at the dialysis centre (15). It should be noted that the data on long-term survival may be misleading, and require attention when interpreting, since patients are rarely treated with PD for more than 5 years. They frequently switch to another replacement therapy, which analyses often interpret as a failure of PD, and take it into account when estimating long-term survival. In 2013, 12.3% of PD patients died in Slovenia (17).

Several factors have been known to affect the survival of PD patients. A number of factors, such as age, diabetes and chronic renal failure etiology, are unchangeable and cannot be affected. We should focus on the factors that can be changed and that affect the long-term prognosis. These are primarily the remaining renal function, the preserved integrity and function of the peritoneal membrane, and peritonitis. We recommend prescribing angiotensin-converting-enzyme inhibitors (ACEI) to all patients who tolerate ACEI well, whether they suffer from hypertension or not, since ACEI helps preserve the remaining renal function. The residual renal function is a good prognostic factor, predicting better outcome in PD and hemodialysis patients. One of the studies found that for every 250 ml of

residual urine production, the 2-year mortality dropped by about 36% (15). Cardiovascular causes account for most deaths in PD patients (18).

Peritonitis-related mortality in PD patients has declined significantly in the past decades due to preventive measures. The rate of cured cases of peritonitis remains high and stable, despite the increasing antibiotic resistance of microorganisms. While less than 5% of episodes result in death, peritonitis still remains a major contributing cause of mortality in approximately 16% of deaths. A peritonitis episode increases the risk of death from an infection, associated cardiovascular diseases and the discontinuation of PD. Peritonitis is the most frequent cause for removing the peritoneal catheter, discontinuing PD and switch to long-term hemodialysis (4,6,18).

10 Conclusion

Peritonitis is a possible and serious, life-threatening complication accompanying PD, which can severely affect the patient. The time between the onset of peritonitis and the commencement of treatment critically determines the course and prognosis of peritonitis, so immediate action is needed. Peritonitis is treated by eliminating the origin of infection, rinsing the abdominal cavity with a 0.9% NaCl solution, and introducing first empiric and then targeted antimicrobial therapy. Peritonitis is the most frequent cause for removing the peritoneal catheter, discontinuing PD and switch to long-term hemodialysis, so its prevention should be the priority of every dialysis centre. Special emphasis should be put on training the patient and their family, especially after a peritonitis episode, since incorrect manipulation of the peritoneal catheter is a frequent cause of the infection.

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